ORFADIN - nitisinone capsule
Rare Disease Therapeutics, Inc.

INDICATIONS AND USAGE
Orfadin® capsules are indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

DOSAGE AND ADMINISTRATION
Treatment with nitisinone should be initiated by a physician experienced in the treatment of hereditary tyrosinemia type 1.
The dose of nitisinone should be adjusted in each patient. The recommended initial dose is 1 mg/kg/day divided for morning and evening administration. Since an effect of food is unknown, nitisinone should be taken at least one hour before a meal. Because of the long half-life of nitisinone, the total dose may be split unevenly as convenient in order to limit the total number of capsules given at each administration. A nutritionist skilled in managing children with inborn errors of metabolism should be employed to design a low-protein diet deficient in tyrosine and phenylalanine. For young children, capsules may be opened and the contents suspended in a small amount of water, formula or apple sauce immediately before use.

Dose Adjustment
Nitisinone treatment should block the flux through the tyrosine degradation pathway at the level of 4-hydroxy-phenylpyruvate dioxygenase. Treatment should lead to normalized porphyrin metabolism (i.e., normal erythrocyte PBG- synthase activity and urine 5 ALA). Succinylacetone should not be detectable in urine or plasma. If the biochemical parameters (except plasma succinylacetone) are not normalized within one month after start of nitisinone treatment, the dose should be increased to 1.5 mg/kg/day. For plasma succinylacetone, it may take up to three months before the level is normalized after the start of nitisinone treatment. Since plasma nitisinone concentration, plasma succinylacetone, urine 5-ALA and erythtocyte PBG-synthase activity are not routinely available, it is appropriate during regular monitoring to follow urine succinylacetone, liver function tests, alpha-fetoprotein, and serum tyrosine and phenylalanine levels. However, during the initiation of therapy and during acute exacerbations, it may be necessary to follow more closely all available biochemical parameters (see Laboratory Tests). A dose of 2 mg/kg/day may be needed, especially in infants, once liver function has improved. This dose should be considered as a maximal dose for all patients.

CONTRAINDICATIONS
None known.

WARNINGS AND PRECAUTIONS

High Plasma Tyrosine Levels
Inadequate restriction of tyrosine and phenylalanine intake can result in elevations in plasma tyrosine. Plasma tyrosine levels should be kept below 500 µmol/L in order to avoid toxic effects to the eyes (corneal ulcers, corneal opacities, keratitis, conjunctivitis, eye pain, and photophobia), skin (painful hyperkeratotic plaques on the soles and palms) and nervous system (variable degrees of mental retardation and developmental delay). In most patients, eye symptoms were transient, lasting less than one week. Six patients had prolonged episodes lasting 16 to 672 days (see **WARNINGS and PRECAUTIONS, Ophthalmologic Care of Patients Treated with Nitisinone**).

Transient Thrombocytopenia and Leucopenia
Patients treated with nitisinone and dietary restriction in clinical trials were observed to develop transient thrombocytopenia (3%), leucopenia (3%) or both (1.5%). One patient, who developed both leucopenia and thrombocytopenia, improved after the dose of nitisinone was decreased from 2 mg/kg to 1 mg/kg. Another patient, who developed thrombocytopenia, had nitisinone stopped for 2 weeks, but platelet values continued to be low for 3 months and slowly returned to normal after 5 months. In all other patients, platelet values and white blood cell counts normalized gradually without documented change in nitisinone dose. No patients developed infections or bleeding as a result of the episodes of leucopenia and thrombocytopenia. **Platelet and white blood cell counts should be monitored regularly during nitisinone therapy.**

Ophthalmologic Care of Patients Treated with Nitisinone
- Slit-lamp examination of the eyes should be performed before initiation of nitisinone treatment.
- Patients who develop photophobia, eye pain or signs of inflammation such as redness, swelling, or burning of the eyes during treatment with nitisinone should undergo slit-lamp reexamination and immediate measurement of the plasma tyrosine concentration.
- A more restricted diet should be implemented if the plasma tyrosine level is above 500 µmol/L.
- Nitisinone dosage should not be adjusted in order to lower the plasma tyrosine concentration, since the HT-1 metabolic defect may result in deterioration of the patient's clinical condition.

Risk of Porphyric Crises, Liver Failure, and Hepatic Neoplasms
Patients with hereditary tyrosinemia type 1 are at increased risk of developing porphyric crises, liver failure, or hepatic neoplasms requiring liver transplantation. These complications of HT-1 were observed in patients treated with nitisinone for a median of 22 months during the clinical trial (liver transplantation 13%, liver failure 7%, malignant hepatic neoplasms 5%, benign hepatic neoplasms 3%, porphyria 0.5%). **Regular liver monitoring by imaging (ultrasound, computerized tomography, magnetic resonance imaging) and laboratory tests, including serum alpha-fetoprotein concentration is recommended. An increase in serum alpha-fetoprotein concentration may be a sign of inadequate treatment, but patients with increasing alpha-fetoprotein or signs of nodules of the liver during treatment with nitisinone should always be evaluated for hepatic malignancy.**

Laboratory Tests
- Plasma nitisinone concentration, urine and plasma succinylacetone levels, urine 5-ALA levels, and erythrocyte PBG-synthase activity were used during clinical trials to guide drug dosage. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a nitisinone concentration of 37 µmol/L (95% confidence interval: 23-51 µmol/L). Assays for plasma nitisinone concentration, plasma succinyl acetone, urine 5-ALA, and erythrocyte PBG-synthase activity are not routinely available in the U.S. However, urine succinylacetone levels can be used to guide drug dose adjustment (see **DOSAGE** and **ADMINISTRATION**).

- Serum alpha-fetoprotein concentrations are generally markedly elevated at the time of diagnosis, and gradually decrease during the course of nitisinone treatment. Increases during therapy may be a sign of inadequate treatment. An exponential increase in serum alpha-fetoprotein concentration should be promptly evaluated for potential liver neoplasia.

- Platelet and white blood cell counts should be monitored regularly because of the risk of transient thrombocytopenia and leukopenia (see **WARNINGS**).

- Serum phosphate should be measured as a screening test for patients with renal involvement at risk of secondary hypophosphatemia and rickets.

- Plasma tyrosine levels should be kept below 500 Âµmol/L in order to avoid toxic effects (see **WARNINGS**).

ADVERSE REACTIONS
In a clinical trial of 207 patients treated with nitisinone for HT-1, the most frequent adverse effects, regardless of causality assessment, occurred in the following organ systems:
Liver and Biliary System:hepatic neoplasm 8%, liver failure 7%.
Visual System:conjunctivitis 2%, corneal opacity 2%, keratitis 2%, photophobia 2%, blepharitis 1%, eye pain 1%, cataracts 1%.
Hemic and Lymphatic:thrombocytopenia 3%, leucopenia 3%, porphyria 1%, epistaxis 1%.
Skin and Appendages:pruritis 1%, exfoliative dermatitis 1%, dry skin 1%, maculopapular rash 1%, alopecia 1%.
Adverse reactions that occurred in less than 1% of the patients, regardless of causality assessment, are:
Body as a Whole:death.
Nervous System:seizures, brain tumor, encephalopathy, headache, hyperkinesia.
Cardiovascular:cyanosis.
Digestive System:abdominal pain, diarrhea, enanthema, gastritis, gastroenteritis, gastrointestinal hemorrhage, melena, tooth discoloration.
Liver and Biliary System:elevated hepatic enzymes, hepatic function disorder, liver enlargement.
Metabolic and Nutritional Disorders:dehydration, hypoglycemia, thirst.
Resistance Mechanism Disorder:infection, septicemia, otitis.
Respiratory:bronchitis, respiratory insufficiency.
Musculoskeletal System:pathologic fracture.
Female Reproductive:amenorrhea.
Psychiatric:nervousness, somnolence.

DRUG INTERACTIONS
No drug-drug interaction studies have been conducted with nitisinone.

USE IN SPECIFIC POPULATIONS

Use In Specific Populations (Pregnancy)
Nitisinone has been shown to have adverse effects on skeletal ossification in animals when given in doses providing exposures less than the human therapeutic dose of 1 mg/kg/day based on body surface area. There are no adequate and well controlled studies in pregnant women. Nitisinone should be used during pregnancy only if the potential benefit justified the potential risk to the fetus.
In pregnant mice given oral gavage doses of 5, 50, 250 mg/kg/day from gestation day 7 through 16, incomplete skeletal ossification of fetal bones was observed with doses ≥5mg/kg/day (exposures less than the human therapeutic dose of 1 mg/kg/day based on relative

body surface area). In pregnant mice given the same doses from gestation day 7 through weaning, gestation length increased in mice given ≥50 mg/kg/day (exposure 4 times the human systemic exposure after 1 mg/kg/day oral dose based on relative body surface area). Decreased pup survival by 9% compared to 5% in untreated controls was observed at 5 mg/kg/day (exposures less than the human systemic exposure after 1 mg/kg/day oral dose based on relative body surface area).
In pregnant rabbits given oral gavage doses of 5, 12, 25 mg/kg/day from gestation day 7 through 19, maternal toxicity and incomplete skeletal ossification of fetal bones was observed with doses of ≥5 mg/kg/day (exposures less than the human therapeutic dose of 1 mg/kg/day based on the body surface area).

Use In Specific Populations (Nursing Mothers)
Although the exposure was not quantified, naive pups that were exposed to Orfadin® via breast milk showed signs of ocular toxicity and lower body weight. This suggests that Orfadin® is excreted via breast milk in rats. It is not known whether nitisinone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitisinone is administrated to a nursing woman.

Use In Specific Populations (Pediatric Use)
Nitisinone has been studied in patients ranging in age from birth to 21.7 years. The median age of enrollment in a study of 207 patients with HT-1 was 9 months.

Use In Specific Populations (Geriatric Use)
Clinical studies of nitisinone did not include any subjects aged 65 and over to determine whether they respond differently from younger subjects. HT-1 is presently a disease of the pediatric population. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this patient population.

OVERDOSAGE
Accidental ingestion of this drug by individuals eating normal diets not restricted in tyrosine and phenylalanine will result in elevated tyrosine levels. In volunteers given a single 1 mg/kg dose of nitisinone, the plasma tyrosine level reached a maximum of 1200 µmol/L from 48 to 120 hours after dosing. After a washout period of 14 days, the mean value of plasma tyrosine was still 808 µmol/L. Fasted follow-up samples obtained from volunteers several weeks later showed tyrosine values back to normal. Nitisinone was generally well tolerated in these studies. There were no reports of changes in vital signs or laboratory data of any clinical significance. One patient did report sensitivity to sunlight. Tyrosinemia has been associated with toxicity to eyes, skin, and the nervous system (see **WARNINGS**).
No information about specific treatment of overdose is available. Restriction of tyrosine and phenylalanine in the diet should limit toxicity associated with tyrosinemia. Patients should be monitored for potential adverse events (see **ADVERSE REACTIONS**).

DESCRIPTION
Orfadin® capsules contain nitisinone, which is a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase used in the treatment of hereditary tyrosinemia type 1 (HT-1).
Nitisinone occurs as white to yellowish-white, crystalline powder. It is practically insoluble in water, soluble in 2M sodium hydroxide and in methanol, and sparingly soluble in alcohol.
Chemically, nitisinone is 2-(2-nitro-4-trifluoromethylbenzoyl) cyclohexane-1,3-dione, and the structural formula is:

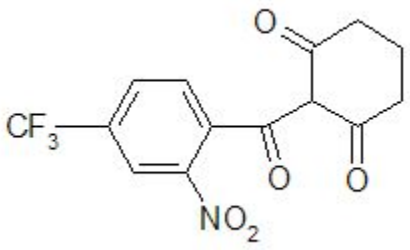

Figure 1. The molecular formula is $C_{14}H_{10}F_3NO_5$ with a relative mass of 329.23
Orfadin® is a hard white-opaque capsule, marked as 2 mg, 5 mg or 10 mg strengths of nitisinone and is intended for oral administration. Each capsule contains 2 mg, 5 mg or 10 mg nitisinone, plus pregelatinized starch. The capsule shell is gelatin and titanium dioxide and the imprint is an iron oxide.

Rx only
See Package Insert
Store refrigerated
2-8° C (36-46° F)

Manufactured by:
Apoteket AB, Sweden, for
SWEDISH ORPHAN INTERNATIONAL AB,
Sweden

Orfadin® Capsules
(nitisinone)
2 mg

For Oral Use

60 capsules
NDC 66607-1002-6

Distributed by:
Rare Disease Therapeutics Inc.
2550 Meridian Blvd., Suite 150
Franklin, TN 37067

541101-01 2001011-02
Expiration Date:
Lot:

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Manufactured by:
Apoteket AB, Sweden, for
SWEDISH ORPHAN INTERNATIONAL AB,
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Orfadin® Capsules
(nitisinone)
5 mg

For Oral Use

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